Original Article

Cross-prevalence of migraine and bipolar disorder


Objective: In two related studies, we explored the prevalence of migraine and its associated clinical characteristics in patients with bipolar disorder (BD) as well as psychiatric morbidity in patients treated for migraine.

Method: The first study included 323 subjects with BD type I (BD I) or BD type II (BD II), diagnosed using the Schedule for Affective Disorders and Schizophrenia, Lifetime version (SADS-L) format, or the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). Migraine history was assessed by means of a structured questionnaire. In a second sample of 102 migraine patients, we investigated current and lifetime psychiatric morbidity using the SADS-L. Statistical analyses were conducted using nonparametric analysis and log-linear models.

Results: A total of 24.5% of BD patients had comorbid migraine; those with BD II had a higher prevalence (34.8%) compared to BD I (19.1%) (p < 0.005). BD patients with comorbid migraine had significantly higher rates of suicidal behaviour, social phobia, panic disorder, generalized anxiety disorder, and obsessive-compulsive disorder (all p < 0.05). In the sample of migraine patients, 34.3% had a current psychiatric diagnosis, and 73.5% had a lifetime psychiatric diagnosis. The prevalence of BD I was 4.9%, and 7.8% for BD II.

Discussion: Migraine is prevalent within the BD population, particularly among BD II subjects. It is associated with an increased risk of suicidal behaviour and comorbid anxiety disorders. Conversely, migraine sufferers have high rates of current and lifetime psychopathology. A greater understanding of this comorbidity may contribute to our knowledge of the underlying mechanisms of BD.

Migraine is defined by the International Headache Society as a recurrent headache disorder, with headaches lasting 4–72 hours, with unilateral location and pulsating quality, aggravated by routine physical activity, and associated with nausea and/or photophobia and phonophobia (1). The classification of migraine includes different subtypes; the most frequent are migraine with aura and without. Estimates of annual prevalence of migraine in the general population range from 3.3% to 21.9% for women and from 0.7% to 16.1% for men (2).
An association between migraine and affective disorders has been noted by several groups who have shown higher lifetime rates of major depression, bipolar disorder (BD), and anxiety disorders in patients with migraine (3–8), as well as an increased suicide risk (3, 9). Moreover, an association between migraine and bipolar affective temperament was recently reported by Fasmer et al. (10).

Migraine is also more common in patients with BD. Several authors have reported migraine prevalence rates as high as 39% (11, 12), almost twice those found in the general population, with associated clinical features such as an earlier onset of BD, a higher prevalence of BD type II (BD II) diagnosis, an increased comorbidity with anxiety disorders, and atypical symptoms of depression (11, 13–15).

Migraine and BD share several characteristics, such as an episodic course, an increased vulnerability to stress, response to antiepileptic drugs, and a positive family history of both migraine and affective disorders. Furthermore, a recent study reported that having a first-degree relative with BD increases the likelihood of having migraine among patients with unipolar depression [odds ratio (OR) = 4.3] and BD (OR = 2.9) (16).

BD and migraine are currently conceptualized as polygenic multifactorial diseases, having both genetic and environmental causative factors. Both disorders have been linked to disturbances in the serotonergic (17–19), dopaminergic (20, 21), and glutamatergic systems (22). A genome-wide linkage study of comorbid BD and migraine recently reported an overlapping susceptibility for both disorders (23). Furthermore, substantial evidence points toward alterations in sodium and calcium channels in the pathophysiology of BD (24, 25) and migraine (26–28). These studies, among others, view migraine as a channelopathy (29), or a disease of neural excitability with a genetically determined lowered threshold for the triggering of attacks (30).

Cortical spreading depression—a slowly propagating wave of neuronal and glial depolarization that spreads across the cortex with a speed of 3–5 mm/min, associated with tissue hypoxia, neuronal swelling, and temporary loss of dendritic spines (31)—is now generally accepted as the biological basis of most types of migraine (32). Other mediators involved in migraine pathogenesis include nitric oxide (33), calcitonin gene-related peptide and substance P (34–36), vasointestinal polypeptide (35, 37, 38), adypocyte-secreted cytokines (adipolecytokines) (39), and orexines (40).

All these conditions seem to point to an overlap in the underlying pathophysiology; however, the mechanisms of comorbidity between migraine and psychiatric disorders remain elusive. An understanding of these correlates is relevant due to the fact that patients with both conditions use health resources in an extended way and because the recognition and treatment of comorbid conditions improve the prognosis of both disorders (41, 42).

To further evaluate the relationship between migraine and psychiatric disorders, we conducted two studies: (i) an analysis of the clinical and demographic characteristics of BD patients with respect to their migraine status, and (ii) an analysis of the psychiatric correlates in a sample of migraine patients.

Methods

Patient selection and assessment

Migraine comorbidity in BD. The sample was composed of two populations: the Maritime Bipolar Registry (MBR) (43) and the Bipolar Disorder Database from the McGill University Health Center (MUHC). The MBR is a community-based project in the Maritime Provinces of Canada (43). At the time of analysis, it included 370 subjects with the following diagnoses: BD type I (BD I) (n = 235), BD II (n = 100), BD not otherwise specified (NOS) (n = 6), and schizoaffective disorder (n = 29). Patients were informed about the opportunity to participate through their treating clinicians. Following detailed description and discussion of the study with potential subjects, written informed consent was obtained. The diagnostic interviews were performed by pairs of clinicians (research nurse, psychiatrist, or clinical research fellow), and the diagnostic information was then reviewed in blind fashion in consensus meetings of the research team. The diagnostic interviews followed the Schedule for Affective Disorders and Schizophrenia, Lifetime version (SADS-L) format (44). The diagnoses were based on both Research Diagnostic Criteria (45) and DSM-IV criteria. Medical comorbidity was ascertained based on previous diagnosis and treatment for each medical condition. All subjects were assessed in the maintenance phase of their treatment, when fully or partially euthymic.

The diagnosis of migraine followed the guidelines of the International Headache Society (46) and was corroborated by a standard questionnaire (ID Migraine) (47). This questionnaire was mailed to all the participants in the MBR. We obtained a response close to 60%; a total of 214 subjects returned the questionnaire and agreed to participate in this project.
The MUHC group included 109 consecutive patients with BD I (n = 78) and BD II (n = 31) diagnoses followed in a tertiary-care program. The patients were interviewed by an experienced clinician using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (48) as the screening instrument, and diagnosed according to the DSM-IV criteria. Migraine diagnosis was also made according to International Headache Society criteria (46). All subjects gave written informed consent to participate in the project.

Psychiatric comorbidity in migraine. The sample was composed of 102 patients interviewed at a specialty migraine clinic where the migraine diagnosis is based on the International Headache Society criteria (46). Patients were randomly chosen from the clinic population and invited to participate in the study by their treating neurologist. Following discussion of the study with eligible subjects, written informed consent was obtained from all participating individuals. Patients who gave consent to participate were interviewed by the same investigator (AO). The diagnostic interviews followed the SADS-L format. Current and lifetime best-estimate psychiatric diagnoses were based on both Research Diagnostic Criteria (45) and DSM-IV criteria, and case note information was obtained. Family history for migraine and mood disorders was also obtained. Diagnostic information was reviewed in a blind fashion using clinical data from 10 randomly chosen cases in consensus meetings of the research team, following the same procedure as in the MBR.

Statistical analysis

To test the differences in clinical characteristics among BD patients with and without migraine, we used nonparametric tests—chi-square ($\chi^2$) and Kruskal-Wallis (KW)—as appropriate. To test for possible differences between the two bipolar samples (MBR and MUHC), we employed log-linear models with stratification by the site.

For the second part of the study, we conducted descriptive data analyses. All analyses were done using the BMDP Statistical Analysis Software Package (49).

Results

Migraine comorbidity in BD

Descriptive characteristics of the BD samples. A total of 214 BD patients (65.4% women and 34.6% men) from the MBR agreed to participate, with a mean age of 51.5 ± 11.9 years. Out of this total, 126 participants (58.9%) had a BD I diagnosis, 61 (28.5%) had a BD II diagnosis, and 27 (12.6%) had been diagnosed with BD NOS or schizoaffective disorder. A total of 53 (24.8%) patients had comorbid migraine.

A total of 109 BD patients (54.1% women and 45.9% men) from the MUHC agreed to participate, with a mean age of 46.4 ± 13.5 years. A total of 78 participants (71.6%) had a BD I diagnosis and 31 (28.4%) had a BD II diagnosis; 26 (23.9%) patients had comorbid migraine. Nonparametric tests showed no statistical significance in the comparison of the descriptive characteristics between the two samples.

The total sample included 323 BD patients (61.6% women and 38.4% men) with a mean age of 49.8 ± 12.7 years. A total of 79 (24.5%) patients had comorbid migraine; 73% had migraine with aura (n = 58, 17.9% of the total sample). No significant differences were observed between men (n = 25, 20.2%) and women (n = 54, 27.1%) (p = 0.1). A total of 204 participants (63.1%) had a BD I diagnosis, 92 (28.5%) had a BD II diagnosis, and 27 (8.4%) were diagnosed with BD NOS or schizoaffective disorder. The prevalence of migraine was 19.2% in BD I and 34.8% in BD II subjects [$\chi^2 (1) = 8.53, p = 0.003$].

Clinical characteristics of BD patients according to their migraine status. Table 1 shows a comparison of the characteristics of BD patients according to their migraine status. Migraine was associated with diagnostic subtype [OR = 2.2; 95% confidence interval (CI): 1.2–3.9], history of suicidal behaviour (OR = 1.7; 95% CI: 1.0–3.0), social phobia (OR = 3.8; 95% CI: 1.9–7.4), panic disorder (OR = 4.3; 95% CI: 2.3–7.8), obsessive-compulsive disorder (OCD) (OR = 2.1; 95% CI: 0.9–4.6), generalized anxiety disorder (GAD) (OR = 2.1; 95% CI: 1.1–3.7), and lower body mass index (BMI) (KW = 4.5, p < 0.05). These associations were consistent across the two samples (MBR and MUHC). The rest of the variables did not show statistical significance (p > 0.05).

To test for possible differences of these associations between the sites, we performed a three-way analysis using log-linear models (results not shown). The log-linear model analysis confirmed the consistency of the results across the two samples. It also confirmed that the increased prevalence of migraine among BD II patients was not related to increased rates of BD II among women [$\chi^2 (3) = 3.68, p = 0.29$].
Psychiatric comorbidity in migraine

A total of 102 migraine patients were included in the study (75.5% women and 24.5% men). The most common diagnosis was migraine without aura (83.3%). The mean age of the sample was 45.7 ± 11.7 years, the reported age at onset of migraine was 20.7 ± 10.7 years, and the age at onset of any psychiatric comorbid disorder was 11 years later (31.7 ± 12.4 years). A migraine diagnosis preceded a diagnosis of psychiatric illness in 78.6% (n = 59) of the affected subjects (n = 75), whereas a prior psychiatric diagnosis preceded a migraine diagnosis only in 14.6% of the sample (n = 11), and both diagnoses were made during the same year in 6.7% of the sample (n = 5). A total of 66 patients (64.7%) had one or more first-degree relatives also diagnosed with migraine (with or without aura), and 57 patients (55.9%) had one or more first-degree relatives diagnosed with a psychiatric disorder.

Current psychiatric diagnoses in migraine patients. A total of 35 subjects (34.3% of the sample) had a current psychiatric diagnosis (Table 2). The most frequent diagnoses among mood disorders were major depressive disorders and BD II. Among anxiety disorders, the most frequent diagnosis was GAD, followed by phobic disorder. Ten subjects (9.8%) had more than one anxiety disorder diagnosis. Twenty-four subjects (23.5%) had both current mood and anxiety disorder diagnoses.

Lifetime psychiatric diagnoses in migraine patients. A total of 75 subjects (73.5% of the sample) had a lifetime psychiatric diagnosis (Table 2). Major...
depressive disorders and BD II were the most prevalent diagnoses among mood disorders. GAD, panic disorder, and phobic disorder showed the highest prevalence among anxiety disorders. Nine subjects (8.8%) presented more than one mood disorder diagnosis, 13 subjects (12.7%) presented more than one anxiety disorder diagnosis, and 43 subjects (42.1%) had presented both mood and anxiety disorder diagnoses in their lifetime. The prevalence of psychotic symptoms was higher among those patients with migraine with aura (17.6%) compared to those without aura (2.3%) \[\chi^2 (2) = 7.34, p < 0.05\]. There were no other differences between migraine subtypes and clinical characteristics.

**Other conditions.** In the total sample (n = 102), 8 (7.8%) subjects had a diagnosis of somatization disorder, and 34 subjects (33.3%) presented with an Axis III comorbid disorder. Of these, the most prevalent were asthma (n = 6), cardiovascular disorders (n = 6), and hypothyroidism (n = 6).

A total of 37 subjects (36.3%) had received psychiatric medications for an indication other than the one related to migraine. Eleven subjects (10.8%) had a history of suicidal behaviour, and 7 subjects (6.9%) had been previously admitted to a psychiatric facility.

**Discussion**

We conducted two separate studies to evaluate the relationship between migraine and psychiatric disorders. The first study analyzed the clinical characteristics of BD patients with and without comorbid migraine, and the second investigated current and lifetime psychiatric comorbidity in migraine patients.

We found a higher prevalence of migraine in patients with BD (24.5%), particularly among those with BD II (34.8%), as well as higher rates of suicidal behaviour, panic disorder, GAD, OCD, and social phobia, as previously reported (14, 15). Patients in this subgroup may indeed have a different profile in terms of the clinical course of the disorder and treatment response. Moreover, the lifetime prevalence of migraine with aura in the BD sample was two times higher than that reported in the general population (50).

Likewise, our results showed the existence of a wide range of psychopathology, mood and anxiety disorders in particular, among migraine sufferers. Previous reports have shown that bipolar spectrum disorders had a nearly threefold higher prevalence among migraine sufferers, with a rate of 8–10% (3, 51). Specifically, a study of the bipolar spectrum (BD I, BD II, BD NOS, and cyclothymic disorder) in 1,000 migraine patients reported a lifetime prevalence of 8.6% (52). Our findings report a prevalence of 7.8% for BD II and 4.9% for BD I among migraine patients.

Recent reports have suggested that anxiety disorders may be the most prevalent psychiatric comorbid condition among patients with BD. The ubiquity of anxiety in BD has been conceived as a core dimension of BD, rather than a comorbidity (51), and several studies have suggested that panic disorder in particular may be genetically related to BD (53, 54). Also, several studies have acknowledged the association between social phobia and BD II (55). Our study showed that the bipolar-anxiety comorbidity may be even higher among BD patients with migraine. BD patients with migraine showed a threefold higher prevalence rate for social phobia and panic disorder when compared to those BD subjects without migraine.

In our study, almost 40% of BD patients with migraine showed a history of suicide attempts, which is in accordance with previous studies suggesting that patients with migraine have higher rates of attempted suicide, even when major depression is controlled (3, 56, 57). It is also in keeping with those studies suggesting that 25–60% of all BD patients will attempt suicide at least once in their lifetime (58), particularly BD II patients (59).

The strengths of the study are that our findings are based upon a large sample (comprised of three different large samples) of clinically well-defined cases of both BD and migraine patients, with concordant results across the samples. This enabled us to assess the significance of migraine in BD and to focus on those BD subjects with migraine in order to study the clinical characteristics that could distinguish a specific subgroup. At the same time, although high rates of different psychiatric diagnoses have been reported in those experiencing migraine, no single investigation has explored the cross-prevalence of these conditions.

One of the limitations of the study is that our results represent migraine diagnoses made by a self-assessment questionnaire (ID Migraine). Although the ID Migraine has been shown to be a valid and reliable clinical instrument, it is subject to the usual recall bias of self-report questionnaires. Another limitation is that the interviews for the second part of the study were conducted in a specialized clinic in migraine; it is probable that the patients in this setting have a chronic or more severe form of the disorder, thus reducing the generalizability of the results. In this sense, the presence of Berkson’s bias (selection bias), where participants’ decision to participate may be
correlated with traits that affect the study, should be taken into account for both parts of the study. The absence of comparison groups (particularly a group including patients with major depressive disorder) is a limitation as well.

Since the medical comorbidities associated with BD could influence its outcome through several factors, including quality of life, functioning, and psychological well-being, it is crucial to assess the prevalence and impact of these conditions in BD. Migraine, for instance, may disrupt circadian rhythms and sleep, thus contributing to mood dysregulation; similarly, migraine episodes are frequently triggered by sleep pattern changes. While the association between psychiatric disorders and migraine may or may not be a causal one, a greater understanding of these specific relations may contribute to our understanding of the underlying aetiologies of both conditions, extend our comprehension of the development of psychopathology, and function as a tool for improving nosology. In addition, the study of this comorbidity may well provide strategies to further define the phenotypes associated with BD, thereby advancing our understanding of the genetics of bipolar disorder.

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References